AMENDMENTS TO THE SPECIFICATION:

Please substitute the following for the paragraph beginning on page 3, line 5 and ending on page 3, line 18:

The invention features substantially pure DNA (cDNA or genomic DNA) encoding a protease-activated receptor 3 (PAR3) from vertebrate tissues (SEQ ID NO:1, SEQ ID NO:2, SEQ ID NO: 4 and SEQ ID NO: 5) and degenerate sequences thereof; substantially pure protease-activated receptor 3 polypeptides encoded thereby; as well as amino acid sequences substantially identical to the amino acid sequences SEQ ID NO:3~~, 24, 25, and 26~~ and SEQ ID NO:6~~, 27, and 28~~ from mouse and human, respectively. The invention further comprises fragments of the PAR3 receptor which are activated by thrombin. Such fragments may have the same amino acid sequence as SEQ ID NO:3~~, 24, 25, and 26~~ and SEQ ID NO:6~~, 27, and 28~~ or be at least 80% identical to the amino acid sequences SEQ ID NO:3~~, 24, 25, and 26~~ and SEQ ID NO:6~~, 27, and 28~~.

Please substitute the following for the paragraph beginning on page 4, line 11 and ending on page 4, line 18:

Figs. 1A-1C ~~is~~ are the complete nucleotide and amino acid sequences (SEQ ID NO:1 and SEQ ID NO:3~~, 24, 25, and 26~~, respectively) of the mouse protease-activated receptor 3 gene coding region cDNA. The deduced amino acid sequence of the receptor is provided below the nucleotide sequence and contains 369 amino acids. The deduced amino acid sequence begins at nucleotides 51-53 (ATG = Met) and ends at nucleotides 1158-1160 (TAG = stop).

Please substitute the following for the paragraph beginning on page 4, line 19 and ending on page 4, line 20:

Figs. 2A-2B ~~is~~ are the genomic sequence (containing exon 2) of the mouse protease-activated receptor 3 (SEQ ID NO:2).

Please substitute the following for the paragraph beginning on page 4, line 21 and ending on page 4, line 28:

Figs. 3A-3C ~~is~~ are the nucleotide and deduced amino acid sequences (SEQ ID NO:4 and SEQ ID NO:6~~, 27, and 28~~, respectively) of the human protease-activated gene coding region cDNA. The deduced amino acid sequence is provided below the nucleotide sequence and contains 374 amino acids. The coding region of the cDNA sequence begins at nucleotides 58-60 (ATG = Met) and ends at nucleotides 1180-1182 (TAG = stop).

Please substitute the following for the paragraph beginning on page 4, line 29 and ending on page 4, line 30:

Figs. 4A-4B is the genomic sequence (containing exon 2) of the human protease-activated receptor 3 (SEQ ID NO:5).

Please substitute the following for the paragraph beginning on page 4, line 31 and ending on page 5, line 5:

Fig. 5A shows the alignment of the deduced amino acid sequences (SEQ ID NO: ~~3,~~6, 7, and ~~8, 9, 24, 25, 26, 27 and 28~~) of the ~~mouse PAR3,~~ human PAR3, human PAR1, and human PAR2. To indicate homology, gaps (represented by blank spaces) have been introduced into the five sequences. Transmembrane domains are overlined (TM1-7). Fig. 5B shows the alignment of the hirudin-like portion of human PAR1, PAR2, and PAR3 amino acid sequences.

Please substitute the following for the paragraph beginning on page 16, line 5 and ending on page 16, line 19:

The human PAR3 cDNA used for the functional studies presented below was cloned from a Lamda gt 10 intestinal cDNA library (Clonetech). Features of human PAR3's amino acid sequence are shown in Figs. 5A and 5B by alignment of the deduced amino acid sequence of PAR3 with those of PAR1 and PAR2. Predicted transmembrane (TM) domains are overlined and predicted Asn-linked glycosylation sites in PAR3 are underlined in the figure. The amino terminal exodomains are compared in Fig. 5b, including the cleavage site (^), the tethered ligand domains of PAR1 and PAR2, and the predicted tethered ligand domain of PAR3 (underlined). Also underlined is PAR3's hirudin-like domain (FEEFP) (SEQ ID NO:14). The similar FEEIP (SEQ ID NO:15) and

YEPFW (SEQ ID NO. 16) sequences in hirudin and PAR1, respectively are known to bind thrombin's fibrinogen-binding exosite.

Please substitute the following for the paragraph beginning on page 16, line 20 and ending on page 17, line 2.

The human PAR3 cDNA contained an open reading frame encoding a 374 amino acid putative G protein-coupled receptor (Fig. 3). BLAST search of the Genbank and EST databases revealed this protein to be novel with 28% and 30% amino acid sequence identity to human PAR1 and PAR2 (Fig. 5a, Table I). Its amino terminal exodomain revealed a possible thrombin cleavage site and a striking hirudin-like sequence (Fig. 5b). Like the carboxyl tail of hirudin itself (SEQ ID NO:9), PAR1's hirudin-like sequence is known to dock with thrombin's fibrinogen binding exosite, an interaction important for efficient PAR1 cleavage by thrombin (Vu, T. –K.H. et al. (1991) Nature 353:674-677; Liu, L. et al. (1991) J. Biol. Chem 266:16977-16980; Mathews, I.I. et al. (1994) Biochem 33 3266-79; Ishii, K. (1995) J. Biol. Chem 270:16435-16440, which references are herein incorporated by reference in their entirety). These observations strongly suggested that this new receptor was a novel thrombin receptor.

Please substitute the following for the paragraph beginning on page 21, line 13 and ending on page 22, line 9.

cDNAs were subcloned into the mammalian expression vector pBJ1. For receptor cleavage studies Cos 7 cells were transfected using DEAE-dextran and thrombin-mediated loss of M1 antibody (Kodak) binding to the FLAG epitope of the cell surface using a procedure described by Ishii et al. (Ishii, K. et al. (1993) *supra*). Over 95% of M1 antibody binding was transfection-dependent in this system. Cells were incubated for 5 min. at 37°C in the presence (open columns) or absence (closed columns) of 20nM thrombin (Fig. 6). For biochemical identification of the cleavage site, cleavage of soluble PAR3 amino terminal exodomain by thrombin was assayed as follows. A recombinant PAR3 soluble exodomain was prepared in which the amino terminal exodomain residues 21-94 were sandwiched between a translational start and hexahistidine tag (i.e. MG- [*PAR3* 21-94] -VEHHHHHH ~~(SEQ ID NO:29)~~; where VEHHHHHH is SEQ ID NO:18). The

recombinant protein was expressed as a soluble polypeptide in *E. coli*, purified, and analyzed before and after thrombin cleavage as previously described for the analogous region of PAR1 (Ishii, K. (1995) J. Biol. Chem. 270:16435-16440). Recombinant soluble amino terminal exodomain was cleaved in solution with 50nM thrombin for 1h at 37°C, then analyzed by SDS-PAGE. Even prolonged incubation with a high concentration of thrombin yielded only one detectable cleavage event indicting that only one thrombin cleavage site exists in the PAR3 exodomain. Amino acid sequencing of the cleavage products revealed only a single new amino terminus with the sequence TFRG ~~[(see Fig.1b)]~~(see Fig. 3, amino acids 39-42 of SEQ ID NO:6). Thus, thrombin recognizes and cleaves PAR3 in the amino terminal exodomain between amino acids K38 and T39 with high specificity.

Please substitute the following for the paragraph beginning on page 23, line 26 and ending on page 24, line 13:

The EC_{50} for thrombin signaling through PAR3 in this system was approximately 0.2 nM, comparable to that seen with PAR1 and well within physiologically achievable thrombin concentrations (FIG 8). γ-thrombin, which is defective in its anion-binding exosite (Rydel, T.J. et al. (1994) J. Biol. Chem. 269:22000-22006), was two log units less potent than α-thrombin (EC_{50} = 20nM; Fig. 9). Similarly, incubation of α-thrombin with the fibrinogen binding exosite blocker hirugen (Skrzypczak, J.E. et al. (1991) J. Mol. Biol. 221:1379-1393) right-shifted the dose response curve two logs (now shown). Alanine substitution at F 48 and E 49 in PAR3's hirudin-like sequence, residues predicted to dock with thrombin's fibrinogen-binding exosite by analogy with hirudin and PAR1 (Fig. 5B) also caused a decrease in thrombin signaling by PAR3. These data strongly suggest that PAR3 interacts with thrombin in a manner similar to PAR1 (Mathews, I. I., et al. (1994) Biochem. 33:3266-3279). Specifically, it is likely that PAR3 amino acids 48-52 (FEEFP, SEQ ID NO:14) dock with thrombin's fibrinogen-binding exosite while amino acids 35-38 (LTPK, SEQ ID NO: [[15]] 26) dock with thrombin's active center leading to cleavage of the K 38-T 39 peptide bond.

Please substitute the following for the paragraph beginning on page 24, line 21 and ending on page 25, line 2:

Peptides homologous to the tethered domain of PAR3 may be tested as potential agonists of PAR3 activity. Two peptides TFRGAP (SEQ NO:[[16]] 27) and TFRGAPPNS (SEQ ID NO:17) were synthesized and tested for their ability to mimic the action of thrombin by causing PAR3 signaling as measured by phosphoinositide hydrolysis. Cos 7 cells expressing human PAR3 were incubated with the peptides at concentrations up to 100 μM. Phosphoinositide hydrolysis was not observed to be above control levels indicating that the synthetic peptides caused no detectable signaling by PAR3 under these conditions, whereas an EC_{50} of 0.2 nM was determined for α-thrombin under the same assay conditions. These results demonstrate that monitoring phosphoinositide hydrolysis provides a useful means for assessing potential agonists for activity on PAR3 signaling for use as potential pharmaceutics.

Please substitute the following for the paragraph beginning on page 33, line 1 and ending on page 33, line 27

Antibodies to PAR 3 are useful antagonists which can be formulated as indicated above. Other therapeutically useful antagonists are peptides derived from PAR3 that bind to and block thrombin and include formulation comprising a pharmaceutically acceptable carrier and one or more of the following:

(1) the isolated sequence LPIKTFRGAPPNSFEEFPFSALE (SEQ ID NO:19);

(2) uncleavable thrombin inhibitor LPIKPFRGAPPNSFEEFPFSALE (SEQ ID NO:20) where the PAR 3 cleavage site P1' is mutated to block cleavage;

(3) uncleavable thrombin inhibitor LPI (hR) TFRGAPPNSFEEFPFSALE (SEQ ID NO:21) where the PAR 3 cleavage site P1 is mutated to block cleavage;

hR is beta-homoarginine (the extra methylene group is in the main chain);

(4) uncleavable thrombin inhibitor (dF) PRPFRGAPPNSFEEFPFSALE (SEQ ID NO:22) where the good active site binding sequence dFRP is substituted for LPIK (SEQ ID NO:23); dF is D-Phenylalanine;

(5) any of (1) – (4) above where all or part of the sequence TFRGAPPNS (SEQ ID NO:17) is replaced with spacer sequence such as GGG;

(6) variations and combinations of (1) – (5) which act as antagonists.